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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/340,196	KATO ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51,53,54,56,59 and 68-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51, 53, 54, 56, 59 and 68-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed September 3, 2004 is acknowledged.

2. Claims 76 and 77 were amended. Claims 51, 53, 54, 56, 59 and 68-77 are pending and examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The objection to claims 76 and 77 is withdrawn in view of the amendments to the claims.

Claim Rejections Withdrawn:

5. The rejection of claims 51, 53, 54, 56, 59 and 68-75 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record, for lack of a description of any predetermined ratios for reference samples, is withdrawn upon further consideration.

Claim Rejections Maintained:

6. Claims 51, 53, 56, 59 and 68-77 are/remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record. The claim(s) contains subject matter that was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the amendment to the claims introduces new matter into the specification.

Applicants' arguments have been carefully considered, but fail to persuade. Applicants assert that it is not necessary in general to provide working examples in order to provide written description support for claimed matter. However, the previous Office action did not specifically cite the lack of working examples as the grounds of rejection under written description. The specification does not contain the specific recitation that is present in the claims "that the sample is determined to be malignant when the calculated ratio is significantly higher or lower than that of the reference fluid sample of the normal thyroid and is significantly higher or lower than that of the reference fluid sample of the benign thyroid". To find indirect support, the working examples as demonstrated by Figures 1-5 were examined. However, none of these provided examples that provided support for the claimed methods with respect to the ratio being significantly higher or lower than that of the reference fluid sample of the normal thyroid and is significantly higher or lower than that of the reference fluid sample of the benign thyroid. Applicants have also pointed to specific passages in the specification at pages 27, 31-33. However, support is not found in these cited passages. Therefore, the rejection is maintained, because, while, the specification teaches the case where the ratio of the lectin-reactivity for a malignant thyroid disease differs from the ratio of benign and from normal, where the benign and normal do not appear to be different from each other (Figures 1 and 2); or the case where the ratio of lectin-reactivity of a benign condition is different from normal and the malignant thyroid disease, where the normal and malignant do not appear to be different from each other (Figure

3), the scope of the claims however, is not in accordance with these two situations. The claims include the possibility that malignant thyroid disease ratio is higher than the normal ratio, but lower than the benign ratio; or the possibility that the malignant thyroid disease ratio is lower than the normal ratio, but higher than the benign ratio. These two possibilities are not supported by the specification as originally filed. Therefore, the amendment to the claims introduces new matter into the specification.

7. Claims 51, 53, 54, 56, 59 and 68-77 are/remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the claimed methods are not described to the extent that the claimed methods read on methods comprising the use of "specific antibodies capable of binding to a specific structure of a sugar chain of a first type of thyroglobulin". Additionally, with respect to claim 76, the claimed methods are not described to the extent that the claimed methods read on methods comprising the use of "specific antibodies" that are "reactive with an Lewis type sugar chain". With respect to claim 77, the clamed methods are not described to the extent that the claimed methods read on methods comprising the use of "specific antibodies" that bind to a sugar chain with a specific structure found in thyroglobulin which is produced by a carcinoma cell.

Applicants' arguments have been carefully considered, but fail to persuade. Applicants assert that it is not necessary in general to provide working examples in order to provide written

description support for claimed matter. However, the basis for the rejection is that the structure of the antigens to which the antibodies bind have not been described. This is especially true for claims 76 and 77, where the antibody is one reactive with a Lewis type sugar chain or where an antibody would bind to a specific structure found in thyroglobulin produced by a carcinoma cell. Applicant indicated a contemplation of antibodies on page 6 of the specification in the interview of 14 July 2004, however, the specification fails to teach that any of the specific antibodies would be useful in distinguishing a first type of thyroglobulin from a second type of thyroglobulin or in specifically binding the a specific structure found in thyroglobulin produced by a carcinoma cell.

8. Claims 51, 53, 54, 56, 59, 68, 69, and 74 reamin rejected under 35 U.S.C. 103(a) as being unpatentable over either Nakamura (U.S. Patent 5,571,729; issued 11/5/1996) or Satomura (U.S. Patent 5,780,247; issued 7/14/1998; effective filing 1/5/1991) in view of either Yamamoto (of record), Tarutani (of record) or Survilo (Survilo, L.I. et al., Vestsi Akademii Navuk Belarusi, Seryya Khimichnykh Navuk, 4: 103-107, 1997; abstract only) for the reasons of record.

Applicants' arguments have been carefully considered, but fail to persuade. In response to applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants' arguments are directed to the deficiencies of Yamamoto and of Tarutani. However, the basis of the rejection is that combination of the teachings of either Nakamura or Satomura with any of Yamamoto, Tarutani or Survilo renders

the claimed methods obvious over the prior art. Thus, either of Nakamura or Satomura teaches methods for using lectins to differentiate between different classes of glycoproteins and either reference teaches methods for measuring the amounts of different types glycoproteins that are different with respect to their lectin reactivity, and also the total amounts of the glycoprotein of interest. The teachings of either Yamamoto, Tarutani or Survilo demonstrate that lectin reactivity of thyroglobulin may be used to differentiate thyroglobulin derived from malignant thyroids from either benign or normal thyroids. Therefore, the prior art as a whole renders obvious the claimed inventions. The previous rejection is reiterated below:

The claimed inventions are drawn to methods for determining malignancy of a thyroid tumor. The claimed methods comprise measuring the amounts of 1 of two types of thyroglobulin and also measuring the total amount of thyroglobulin. All of the claimed inventions comprise the use of a specific lectin or specific antibody capable of binding to a specific structure of a sugar chain of a first type of thyroglobulin, but not capable of binding to a sugar chain of a second type of thyroglobulin. All of the claimed inventions comprise the use of an anti thyroglobulin antibody that binds to both types of thyroglobulin. Claims 54, 59, 69 and 74 comprise a separation step, where the lectin-thyroglobulin complex or sugar-specific antibody-thyroglobulin complex is separated prior to measuring the amount of the complex. Claims 56, 59, 68 and 74 may comprise a step of directly measuring the amount of the second type of thyroglobulin (that does not bind to the lectin or the sugar-specific antibody). Claims 56, 59, 68, 69, and 74 comprise calculating a ratio of the amount of the first type of thyroglobulin to the total amount of thyroglobulin; or a ratio of the amount of the second type of thyroglobulin to the

total amount of thyroglobulin. Claims 51, 53, and 54 comprise calculating a ratio of the amount of the first type of thyroglobulin to the total amount of thyroglobulin. Malignancy is determined when the calculated ratio is significantly higher or lower than a ratio from a reference sample of normal and higher or lower than a reference sample of benign.

Nakamura teaches a method for measuring two different types of glycoproteins (example is human chorionic gonadotropin (hCG) comprising adding to a sample containing the hCG an antibody that binds to both types of hCG and a lectin that selectively binds to only one of the two types of hCG. Nakamura teaches separation of the resulting complexes from each other by HPLC and teaches measuring the amounts of the two types in the sample (see col. 2, lines 23-40). Satomura teaches and claims methods for separating and simultaneously measuring the total of and specific components of analytes having similar structures, where the analytes have sugar chains, comprising mixing a sample with a first affinity substance that binds to all of the analytes in the sample and a second affinity substance that binds to at least one of the analytes but does not bind to at least one of the other analytes, where the second affinity substance may be a lectin and the first affinity substance may be an antibody (see claims 1, and 5-9). Thus, either Nakamura or Satomura teaches methods for measuring the amounts of different types glycoproteins that are different with respect to their lectin reactivity, and also the total amounts of the glycoprotein of interest.

Neither Nakamura nor Satomura teaches methods directed to measuring different types of thyroglobulin based on their differential reactivity to lectins, and neither Nakamura nor Satomura teaches a relationship between differential thyroglobulin lectin-reactivity with malignancy of a thyroid tumor.

However, Yamamoto teaches that thyroglobulin isolated from malignant thyroid tumor tissue has a different DEAE-cellulose ion exchange elution pattern from thyroglobulin isolated from benign and from normal thyroids (page 138, first –2nd col.). Yamamoto teaches that the carbohydrate chains of thyroglobulin derived from the benign tumor had the same structures as those thyroglobulin derived from normal thyroid. Yamamoto teaches that thyroglobulin derived from malignant thyroid tumor contains less sialic acid, contains less high-mannose type carbohydrate moieties, contains oligosaccharides of high molecular mass with repeating Gal-GlcNAc disaccharides and peripheral alpha-fucosyl residues than does thyroglobulin isolated from normal and benign thyroid tissue (page 142, 2nd col – page 143, 1st col). Yamamoto also teaches that using the lectin, ConA, one can differentiate between thyroglobulin isolated from malignant thyroid from thyroglobulin isolated from normal and benign thyroid. ConA affinity chromatography demonstrates that thyroglobulin from malignant thyroids contains more triantenary complex-type oligosaccharides than thyroglobulin from normal thyroids; RCA affinity chromatography demonstrates that thyroglobulin from malignant thyroids has a greater amount of asialo complex-type carbohydrate chains than does thyroglobulin from normal thyroids. Thus, Yamamoto provides teachings that allow one or ordinary skill in the art to predict that lectin affinity may be used as the basis for an assay to differentiate between thyroglobulin secreted from a thyroid tumor from thyroglobulin secreted from a non-cancerous thyroid.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of either Nakamura or Satomura in the measurement of differential lectin reactivity to determine if a thyroglobulin was derived from a

patient with a malignant thyroid tumor from a patient with either a benign or a normal thyroid, because Yamamoto teaches that either ConA-reactivity or RCA-reactivity may be used to distinguish thyroglobulin derived from malignant thyroid tumors from thyroglobulin derived from benign or normal thyroids.

Tarutani teaches that the percent of total thyroglobulin that binds to Con-A is different for trabecular carcinoma compared to either follicular adenoma (a benign condition) or normal thyroid tissue (see page 855, Table II). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of either Nakamura or Satomura in the measurement of differential lectin reactivity to determine if a thyroglobulin was derived from a patient with a malignant thyroid tumor from a patient with either a benign or a normal thyroid, because Tarutani teaches that ConA-reactivity may be used to distinguish thyroglobulin derived from malignant thyroid tumors from thyroglobulin derived from benign or normal thyroids.

Survilo teaches that thyroglobulin samples from cancerous thyroids did not bind as strongly to ConA-Sepharose as did those from normal or goiterous thyroids. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of either Nakamura or Satomura in the measurement of differential lectin reactivity to determine if a thyroglobulin was derived from a patient with a malignant thyroid tumor from a patient with either a benign or a normal thyroid, because Survilo teaches that ConA-reactivity may be used to distinguish thyroglobulin derived from malignant thyroid tumors from thyroglobulin derived from benign or normal thyroids. Because either of Yamamoto, Tartani or Survilo teach that there is differential lectin reactivity between

thyroglobulin from malignant and benign or normal thyroids, a different ratio of one type of glycoslated thyroglobulin to a second type of glycosylated thyroglobulin would be expected using the method of Katoh. Furthermore, Tarutani specifically demonstrates that for Con-A reactivity, there are different ratios of bound to unbound for thyroglobulin derived from normal versus cancerous thyroid samples in Table II on page 855.

9. Claims 70 and 71 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Katoh (U.S. Patent 5,591,589; issued 1/7/1997) in view of either Yamamoto (of record), Tarutani (of record) or Survilo (Survilo, L.I. et al., Vestsi Akademii Navuk Belarusi, Seryya Khimichnykh Navuk, 4: 103-107, 1997; abstract only) for the reasons of record.

Applicants' arguments have been carefully considered, but fail to persuade. In response to applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants' arguments are directed to the deficiencies of Yamamoto and of Tarutani. However, the basis of the rejection is that combination of the teachings of Katoh with any of Yamamoto, Tarutani or Survilo renders the claimed methods obvious over the prior art. Thus, Katoh teaches methods for teaches and claims methods for separating and measuring two or more forms of glycoproteins that are different in sugar chain structure but have essentially the same protein structure, comprising mixing a sample with a lectin capable of recognizing the specific sugar chain structure of at least one of these glycoproteins to be measured, and a first antibody which has a property of bind to

all the glycoproteins but does not bind to glycoproteins having the lectin attached thereto; and separating and measuring glycoproteins having the first antibodies attached and glycoproteins having no first antibody attached. Additionally, Katoh teaches that a second antibody may be employed, where the second antibody binds to all of the glycoproteins regardless of whether the lectin is also bound (see claims 1, and 3). Thus, Katoh teaches methods for measuring the amounts of different types glycoproteins that are different with respect to their lectin reactivity, and also the total amounts of the glycoprotein of interest. The teachings of either Yamamoto, Tarutani or Survilo demonstrate that lectin reactivity of thyroglobulin may be used to differentiate thyroglobulin derived from malignant thyroids from either benign or normal thyroids. Because either of Yamamoto, Tartani or Survilo teach that there is differential lectin reactivity between thyroglobulin from malignant and benign or normal thyroids, a different ratio of one type of glycoslated thyroglobulin to a second type of glycosylated thyroglobulin would be expected using the method of Katoh. Furthermore, Tarutani specifically demonstrates that for Con-A reactivity, there are different ratios of bound to unbound for thyroglobulin derived from normal versus cancerous thyroid samples in Table II on page 855. Therefore, the prior art as a whole renders obvious the claimed inventions. The previous rejection is reiterated below:

Claims 70 and 71 are drawn to methods for determining malignancy of a thyroid tumor. The claimed methods comprise measuring the amounts of at least one of two types of thyroglobulin and also measuring the total amount of thyroglobulin. All of the claimed inventions comprise the use of a specific lectin or specific antibody capable of binding to a specific structure of a sugar chain of a first type of thyroglobulin, but not capable of binding to a

sugar chain of a second type of thyroglobulin; and comprise the use of a second antibody that does not bind to a lectin-thyroglobulin complex. Claim 71 comprises the use of an anti thyroglobulin antibody that binds to all types of thyroglobulin, regardless of whether the lectin is also bound. Malignancy is determined when the calculated ratio is significantly higher or lower than a ratio from a reference sample of normal and higher or lower than a reference sample of benign.

Katoh teaches and claims methods for separating and measuring two or more forms of glycoproteins that are different in sugar chain structure but have essentially the same protein structure, comprising mixing a sample with a lectin capable of recognizing the specific sugar chain structure of at least one of these glycoproteins to be measured, and a first antibody which has a property of bind to all the glycoproteins but does not bind to glycoproteins having the lectin attached thereto; and separating and measuring glycoproteins having the first antibodies attached and glycoproteins having no first antibody attached. Additionally, Katoh teaches that a second antibody may be employed, where the second antibody binds to all of the glycoproteins regardless of whether the lectin is also bound (see claims 1, and 3). Thus, Katoh teaches methods for measuring the amounts of different types glycoproteins that are different with respect to their lectin reactivity, and also the total amounts of the glycoprotein of interest.

Katoh fails to teach methods directed to measuring different types of thyroglobulin based on their differential reactivity to lectins, and Katoh fails to teach a relationship between differential thyroglobulin lectin-reactivity with malignancy of a thyroid tumor.

However, Yamamoto teaches that thyroglobulin isolated from malignant thyroid tumor tissue has a different DEAE-cellulose ion exchange elution pattern from thyroglobulin isolated

from benign and from normal thyroids (page 138, first –2nd col.). Yamamoto teaches that the carbohydrate chains of thyroglobulin derived from the benign tumor had the same structures as those thyroglobulin derived from normal thyroid. Yamamoto teaches that thyroglobulin derived from malignant thyroid tumor contains less sialic acid, contains less high-mannose type carbohydrate moieties, contains oligosaccharides of high molecular mass with repeating Gal-GlcNAc disaccharides and peripheral alpha-fucosyl residues than does thyroglobulin isolated from normal and benign thyroid tissue (page 142, 2nd col – page 143, 1st col). Yamamoto also teaches that using the lectin, ConA, one can differentiate between thyroglobulin isolated from malignant thyroid from thyroglobulin isolated from normal and benign thyroid. ConA affinity chromatography demonstrates that thyroglobulin from malignant thyroids contains more triantenary complex-type oligosaccharides than thyroglobulin from normal thyroids; RCA affinity chromatography demonstrates that thyroglobulin from malignant thyroids has a greater amount of asialo complex-type carbohydrate chains than does thyroglobulin from normal thyroids. Thus, Yamamoto provides teachings that allow one of ordinary skill in the art to predict that lectin affinity may be used as the basis for an assay to differentiate between thyroglobulin secreted from a thyroid tumor from thyroglobulin secreted from a non-cancerous thyroid.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of Katoh in the measurement of differential lectin reactivity to determine if a thyroglobulin was derived from a patient with a malignant thyroid tumor from a patient with either a benign or a normal thyroid, because Yamamoto teaches that either ConA-reactivity or RCA-reactivity may be used to distinguish

thyroglobulin derived from malignant thyroid tumors from thyroglobulin derived from benign or normal thyroids.

Tarutani teaches that the percent of total thyroglobulin that binds to Con-A is different for trabecular carcinoma compared to either follicular adenoma (a benign condition) or normal thyroid tissue (see page 855, Table II). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of Katoh in the measurement of differential lectin reactivity to determine if a thyroglobulin was derived from a patient with a malignant thyroid tumor from a patient with either a benign or a normal thyroid, because Tarutani teaches that ConA-reactivity may be used to distinguish thyroglobulin derived from malignant thyroid tumors from thyroglobulin derived from benign or normal thyroids.

Survilo teaches that thyroglobulin samples from cancerous thyroids did not bind as strongly to ConA-Sepharose as did those from normal or goiterous thyroids (an example of a benign condition). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of Katoh in the measurement of differential lectin reactivity to determine if a thyroglobulin was derived from a patient with a malignant thyroid tumor from a patient with either a benign or a normal thyroid, because Survilo teaches that ConA-reactivity may be used to distinguish thyroglobulin derived from malignant thyroid tumors from thyroglobulin derived from benign or normal thyroids.

Because each of the references, Yamamoto, Tarutani or Survilo, teaches that the amounts of thyroglobulin that bind to Con-A are different, one of ordinary skill in the art would have had a reasonable expectation that calculating ratios of the amounts of a first or a second type

thyroglobulin to the total amount of thyroglobulin would demonstrate that malignant thyroid tumors have less thyroglobulin that reacts with Con-A than does either benign or normal thyroid.

10. Claim 73 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Canfield (WO/87/00289;) in view of Yamamoto (of record).

Applicants' arguments have been carefully considered, but fail to persuade. Applicant argues that because Yamamoto fails to teach determining thyroid malignancy by measuring a ratio, that the combination of Canfield with Yamamoto does not render obvious to the claimed methods. This argument is unpersuasive, because Yamamoto teaches proportions of different carbohydrate components for both normal and malignant thyroids in Tables 1 and Tables 2, where it can be clearly seen that as a fraction of the total the different fractions of thyroglobulin differ between normal and malignant thyroids. Therefore, using the method of Canfield with the information provided by Yamamoto renders the claimed method obvious. The previous rejection is reiterated below:

Claim 73 is drawn to a method for determining malignancy of a thyroid tumor, where the methods comprise measuring the amounts of at least one of two types of thyroglobulin and also measuring the total amount of thyroglobulin, where the sample is divided into two portions, with one portion one measures one of two types of thyroglobulin, and with the second portion, one measures total thyrogobulin levels. All of the claimed inventions comprise the use of a specific lectin or specific antibody capable of binding to a specific structure of a sugar chain of a first type of thyroglobulin, but not capable of binding to a sugar chain of a second type of

thyroglobulin; and comprise the use of a second antibody that does not bind to a lectin-thyroglobulin complex. Malignancy is determined when the calculated ratio is significantly higher or lower than a ratio from a reference sample of normal and higher or lower than a reference sample of benign.

Canfield teaches the use of differential lectin-reactivity as the basis for measuring desialated hCG levels (page 15). Canfield also teaches that this method may be used to measure differentially glycosylated thyroglobulin (page 9, lines 20-23). Canfield teaches a method for measuring desialated hCG as a percentage of total hCG in samples from patients having gestational trophoblastic tumors and from patients with a normal pregnancy (page 24, lines 19-24). In order to obtain the data for the ratios of desialated hCG to total hCG, Canfield provides an example where the data is obtained by at least two separate measurements that would have required separating the sample into at least two portions. Canfield teaches that asialated hCG was measured in one instance with a RCA-^{125}I-R525 LIRMA and that total hCG was determined utilizing the B101-R525 IRMA (see page 24, lines 19-24). Therefore, Canfield teaches the method steps of the claimed methods, whereby a sample is divided into two portions.

While Canfield does teach that methods of using lectin-based assays may be used in combination with antibody assays to distinguish and quantitate desialated thyroglobulin from normally glycosylated thyroglobulin, Canfield fails to teach that measuring levels of desialated thyroglobulin is correlated of thyroid malignancy.

However, Yamamoto teaches that thyroglobulin derived from malignant thyroid tumor contains less sialic acid than does the thyroglobulin of normal or benign thyroids, and that RCA-affinity chromatography demonstrates that thyroglobulin from malignant thyroids has a greater

amount of asialo complex-type carbohydrate chains than does thyroglobulin from normal thyroids.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of Canfield in the measurement of differential lectin-reactivity to determine if a thyroglobulin was derived from a patient with a malignant thyroid tumor from a patient with either a benign or a normal thyroid, because Yamamoto teaches that RCA-reactivity may be used to distinguish thyroglobulin derived from malignant thyroid tumors from thyroglobulin derived from benign or normal thyroids.

11. Claim 75 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Katoh (supra) in view of Canfield (WO/87/00289;) and further in view of Yamamoto (supra) for the reasons of record.

Applicants' arguments have been carefully considered but fail to persuade. Applicants argue that Yamamoto fails to teach different ratios of differentially glycosylated thyroglobulin between normal thyroids and malignant thyroids. As discussed above, this does not appear to be the case, because in Tables I and II, Yamamoto clearly shows different proportions of different species of thyroglobulin. The previous rejection is reiterated below:

Claim 75 is drawn to methods for determining malignancy of a thyroid tumor. The claimed methods comprise measuring the amounts of at least one of two types of thyroglobulin and also measuring the total amount of thyroglobulin. All of the claimed inventions comprise the use of a specific lectin or specific antibody capable of binding to a specific structure of a

sugar chain of a first type of thyroglobulin, but not capable of binding to a sugar chain of a second type of thyroglobulin; and comprise the use of a second antibody that does not bind to a lectin-thyroglobulin complex. The claimed methods comprise the measurement of total amount of thyroglobulin, whereby the sample is divided into two portions, with one portion one measures one of two types of thyroglobulin, and with the second portion, one measures total thyrogobulin levels. Malignancy is determined when the calculated ratio is significantly higher or lower than a ratio from a reference sample of normal and higher or lower than a reference sample of benign.

Katoh teaches and claims methods for separating and measuring two or more forms of glycoproteins that are different in sugar chain structure but have essentially the same protein structure, comprising mixing a sample with a lectin capable of recognizing the specific sugar chain structure of at least one of these glycoproteins to be measured, and a first antibody which has a property of binding to all the glycoproteins but does not bind to glycproteins having the lectin attached thereto; and separating and measuring glycoproteins having the first antibodies attached and glycoproteins having no first antibody attached. Thus, Katoh teaches methods for measuring the amounts of different types glycoproteins that are different with respect to their lectin reactivity.

Katoh fails to teach methods directed to measuring different types of thyroglobulin based on their differential reactivity to lectins, and Katoh fails to teach a relationship between differential thyroglobulin lectin-reactivity with malignancy of a thyroid tumor. Additionally, although Katoh teaches that one may measure total amounts of the glycoprotein of interest,

Katoh fails to teach that this step may be done by first dividing a sample into two portions, where one of the portions is used to measure total amount of glycoprotein.

However, Canfield teaches the use of differential lectin-reactivity as the basis for measuring desialated hCG levels (page 15). Canfield also teaches that this method may be used to measure differentially glycosylated thyroglobulin (page 9, lines 20-23). Canfield teaches a method for measuring desialated hCG as a percentage of total hCG in samples from patients having gestational trophblastic tumors and from patients with a normal pregnancy (page 24, lines 19-24). In order to obtain the data for the ratios of desialated hCG to total hCG, Canfield provides an example where the data is obtained by at least two separate measurements that would have required separating the sample into at least two portions. Canfield teaches that asialated hCG was measured in one instance with a RCA-^{125}I-R525 LIRMA and that total hCG was determined utilizing the B101-R525 IRMA (see page 24, lines 19-24). Therefore, Canfield teaches the method steps of the claimed methods. The teachings of Katoh in combination with those of Canfield provide methods where differentially glycosylated thyroglobulin may be measured as a percent of total thyroglobulin.

While Canfield does teach that methods of using lectin-based assays may be used in combination with antibody assays to distinguish and quantitate desialated thyroglobulin from normally glycosylated thyroglobulin, Canfield fails to teach that measuring levels of desialated thyroglobulin is correlated of thyroid malignancy.

However, Yamamoto teaches that thyroglobulin derived from malignant thyroid tumor contains less sialic acid than does the thyroglobulin of normal or benign thyroids, and that RCA-affinity chromatography demonstrates that thyroglobulin from malignant thyroids has a greater

amount of asialo complex-type carbohydrate chains than does thyroglobulin from normal thyroids.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of Katoh in combination with Canfield in the measurement of differential lectin reactivity to determine if a sample of thyroglobulin was derived from a patient with a malignant thyroid tumor from a patient with either a benign or a normal thyroid, because Yamamoto teaches that RCA-reactivity may be used to distinguish thyroglobulin derived from malignant thyroid tumors from thyroglobulin derived from benign or normal thyroids.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 51, 53, 54, 56, 59, 68, 69, and 74 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, and 5-9 of U.S. Patent No. 5,780,247 in view of either Yamamoto (of record), Tarutani (of record) or

Survilo (Survilo, L.I. et al., Vestsi Akademii Navuk Belarusi, Seryya Khimichnykh Navuk, 4: 103-107, 1997; abstract only). The claimed inventions are an obvious species of method that are within the scope of claims 1 and 5-9 of U.S. Patent No. 5,780,247. In view of the teachings of either Yamamoto, Tarutani or Survilo, that thyroglobulin is a glycosylated protein and that thyroglobulin derived from malignant thyroids contains a different glycosylation pattern, and in view of the teachings that this can be observed by measuring differences in lectin-reactivity, the claimed inventions are an obvious species of the methods of claims 1 and 5-9 or U.S. Patent 5,780,247.

Applicants' arguments are unpersuasive for the reasons set forth above in the response to the arguments against the rejections under 103(a) over the cited references.

14. Claims 70 and 71 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3 of U.S. Patent No. 5,591,589 in view of either Yamamoto (of record), Tarutani (of record) or Survilo (Survilo, L.I. et al., Vestsi Akademii Navuk Belarusi, Seryya Khimichnykh Navuk, 4: 103-107, 1997; abstract only). The claimed inventions are an obvious species of method that are within the scope of claims 1 and 3 of U.S. Patent No. 5,591,589. In view of the teachings of either Yamamoto, Tarutani or Survilo, that thyroglobulin is a glycosylated protein and that thyroglobulin derived from malignant thyroids contains a different glycosylation pattern, and in view of the teachings that this can be observed by measuring differences in lectin-reactivity, the claimed inventions are an obvious species of the methods of claims 1 and 3 or U.S. Patent 5,591,589.

Applicants' arguments are unpersuasive for the reasons set forth above in the response to the arguments against the rejections under 103(a) over the cited references.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (571) 272-0833. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 571-1600.

Anne L. Holleran
Patent Examiner

ANA M. HARRIS, PH.D.
PRIMARY EXAMINER
12/28/2004